REMARKS

With this Response, claims 3-8, 11 and 16 have been canceled. Claims 1, 2, 9, 10 and 12-15 are amended. As such, claims 1-2, 9, 10 and 12-15 are currently pending in the application. The amendments find support in the specification and are discussed in the relevant sections below. No new matter is added.

Summary of August 25, 2004 Interview:

Applicant is extremely grateful to Examiner Carolyn Smith and Examiner Ardin Marschel for participating in a telephone interview with Attorney Michael Doyle on August 25, 2004. During the interview, Attorney Doyle briefly discussed the Lincoln et al, Lehman et al., and Schraml et al. references.

In attempting to distinguish the Applicant's claimed invention from the cited references, Attorney Doyle described the Applicant's invention as a control microarray wherein each sample on the array is representative of a known stage of cancer. The utility of such an invention being that a patient in need of a diagnosis could compare his/her tissue sample to the control microarray, find a matching sample and thereby determine the corresponding stage of cancer for the unknown sample.

During the interview, Examiner Marschel expressed concern that such claim coverage could read upon a microarray of unknown cancer stages, i.e., a microarray in a lab comprising a variety of samples wherein each sample happens to represent a different stage of cancer.

With this Response, independent claim 1 has been amended and several claims have been canceled to better clarify the Applicant's claimed invention and to exclude the possibility that the claims could read upon such a microarray as described by Examiner Marschel.

Again, Applicant is extremely thankful to Examiners Smith and Marschel for their participation in the expedition of the prosecution of the pending application.

Claims Rejected Under 35 U.S.C. §112, First Paragraph:

The Office Action rejected claims 1-16 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement, stating:

> The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is necessitated by amendment.
>
> Applicants did not point to any support within the specification, drawings, or claims, as originally filed for the newly amended phrase "wherein each sample of the microarray exhibits a biological characteristic representative of a stage of cancer" as newly stated in amended claims 1, 3, and 4. The abstract states the phrase "each sample represents a different stage of cancer"; however, this does not provide support for *each* sample *exhibiting a biological characteristic representative* of a stage of cancer, which differs in scope. No mention is made as to whether such representative biological characteristics are exhibited in each sample. Because the introduction of "wherein each sample of the microarray exhibits a biological characteristic representative of a stage of cancer" lacks proper written support in amended claims 1, 3, and 4, filed 5/13/04, this phrase is considered NEW MATTER. Claims 2 and 5-16 are also rejected due to their direct or indirect dependency from claims 1, 3, and 4. This rejection is necessitated by amendment. (July 26, 2004 Final Office Action; Pages 2-3).

With this Response, Applicant has canceled independent claims 3 and 4; further, Applicant has amended independent claim 1 to remove the phrase ""wherein each sample of the microarray exhibits a biological characteristic representative of a stage of cancer." As will be outlined below, the current amendments find support throughout the specification. As such, Applicant respectfully requests withdrawal of the rejections under 35 U.S.C. §112, first paragraph.

Claims Rejected Under 35 U.S.C. §112, Second Paragraph:

The July 26, 2004 Office Action rejected claims 1-16 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, stating:

> Claims 1, 3, and 4 recite the phrase "exhibits a biological characteristic representative of a stage of cancer" which is vague and indefinite. It is unclear what criteria and to what degree these criteria must be met for the exhibited biological characteristic to be considered "representative of a stage of cancer." Clarification of the metes and bounds of this phrase via clearer claim wording is requested. Claims 2 and 5-16 are also rejected due to their direct or indirect dependency from claims 1, 3, and 4. (July 26, 2004 Final Office Action; Page 3).

With this Response, Applicant has amended the claims to remove the phrase "...exhibits a biological characteristic representative of a stage of cancer." As will be outlined below, the current amendments find support throughout the specification. As such, Applicant respectfully requests withdrawal of the rejections under 35 U.S.C. §112, second paragraph.

Claims Rejected Under 35 U.S.C. §102:

The Office Action rejected claims 1, 2, 5, 6, 10-13, and 15-16 under 35 U.S.C. §102(e)(2) as being anticipated by U.S. Patent No. 6,553,317 to Lincoln et al., stating:

> This rejection is maintained and reiterated for reasons of record. The amended phrase "wherein each sample of the microarray exhibits a biological characteristic representative of a stage of cancer" in claim 1 is not addressed as it is considered NEW MATTER that must be deleted.
>
> Lincoln et al. disclose the use of bioinformatics to study genes differentially expressed or commonly expressed in different tissues or cell lines, such as normal (normally proliferating cells) and cancerous tissue (abnormally proliferating cells) (col. 1, lines 46-48). Lincoln et al. disclose using a microarray with multiple samples (col. 3, lines 10-12). Lincoln et al. disclose processing clones in groups on a 96-well plastic culture dish with each chamber/well comprising an indentation in the dish to separate samples (col. 12, lines 20-25) which represents a stably associated samples with a distinct, known sublocation on a substrate, as stated in instant claim 1. Lincoln et al. disclose a barcode (identifier) for a lot or 96-well plate whose value is placed in a barcode field of a table in a database (col. 21, lines 30-41) which represents a substrate with an identifier that provides access to a database, as stated in instant claim 1. The samples in a plastic culture dish represent the sample (tissue or cells) being plastic-embedded, as stated in instant claim 10. The information on the plastic culture dish, including precise sample location with lot and well information, is recorded for each sample and given to customers (col. 12, lines 29-36). Lincoln et al. disclose using a relational database system for

storing biomolecular sequence information with biological annotations (col. 2, lines 14-20) including information identifying (identifiers) sequences (col. 2, lines 28-34). Lincoln et al. disclose a system allowing a user to selectively view information regarding sequences and reagent specifications (col. 2, lines 34-37) including a graphical user interface where a query is entered and matches between query and information is displayed (col. 2, lines 46-50). Lincoln et al. disclose using a relational database with tables (col. 15, lines 44-49) including a library table that includes records of each library in the gene expression database including an identifier (LibraryID) (col. 16, lines 7-9). Lincoln et al. disclose the library table as having a "TissueID" attribute that is inherited from a "TissueSpecimen" table) and a "Tissue_Category" attribute as well as a "Lib_Description" attribute including information such as tissue name, disease state, patient age/gender (col. 16, lines 6-32). Lincoln et al. disclose providing thither information about a donor in a "MedicalHistory" table including information such as a problem such as breast cancer, breast, and neoplasm (col. 20, lines 33-40), as stated in instant claim 6. Lincoln et al. disclose using a network to which the network server and clients are connected (col. 13, lines 3-9). Lincoln et al. disclose entries in various results screens may provide links to other information in the database (col. 23, lines 10-13) as stated in instant claim 2. Lincoln et al. disclose each tissue specimen (as uniquely identified by TissueID) may have several diagnoses (i.e. normal, diseased, involved, cancerous) and each donor may provide multiple tissue specimens (col. 19, lines 35-67). This act of providing multiple tissue specimens that ate "cancerous" or "involved" is reasonably interpreted to include specimens from sites of a secondary metastasis of cancer, as stated in instant claim 16. Lincoln et al. disclose different development stages (col. 20, lines 13-14) as stated in claim 11. Lincoln et al. disclose studying or monitoring drug resistance in certain tissue (col. 5, lines 1-3) which represents substantially homogeneous cells (as stated in instant claim 13) and samples from patients treated with a drug (as stated in instant claim 15).

Thus, Lincoln et al. anticipate the limitations in claims 1, 2, 5, 6, 10-13, and 15-16.

Applicants state their amended phrase including the limitation of "wherein each sample of the microarray exhibits a biological characteristic representative of a stage of cancer" is part of the claimed invention. This is confusing as instant claim 5 comprises normally proliferating cells which suggests normal cells that are not representative of a cancerous stage. Applicants state the claimed invention allows for the comparison of a patient's tissue and/or cell sample with the samples of the microarray to determine the progression of the patient's illness. While this statement may be true, such determination of illness progression is considered

> irrelevant in comparison to prior art as this determination is not disclosed in the instant claims.] Applicants state that Lincoln et al. do not disclose a microarray and then state that Lincoln et al. disclose "microarray" in two passages. Lincoln et al. clearly disclose a microarray, as stated in column 3 (line 12), column 8 (line 67), and column 9 (lines 3-4). Applicants state that Lincoln et al. recitation of a microarray does not anticipate an oncology microarray wherein each sample exhibits a biological characteristic representative of a stage of cancer. This is found unpersuasive as such a microarray with each sample exhibiting a biological characteristic representative of a stage of cancer appears to be NEW MATTER and not specifically mentioned in the instant application. Lincoln et al. clearly disclose the study of cancerous tissue and the use of a microarray, as disclosed above. (July 26, 2004 Final Office Action; Pages 4-7).

With this Response, Applicant has amended independent claim 1 and canceled independent claims 3 and 4. Further, independent claim 1 has been amended to better define the Applicant's invention--**the invention being a control oncology tissue microarray comprising samples representing the progression of a type of cancer from an early stage to an advanced stage**. Such a control oncology tissue microarray allows for a side-by-side comparison of an unknown test tissue with the various known samples of the control oncology tissue microarray. The Applicant believes these amendments distinguish the claimed invention from the cited art and has overcome the rejections under 35 U.S.C. §102.

To anticipate a claim, the reference must teach every element of the claim. M.P.E.P. 2131. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California,* 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987); M.P.E.P. 2131. "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.,* 868 F.2d 1226, 1236, 9 U.S.P.Q.2d 1913, 1920 (Fed. Cir. 1989); M.P.E.P. 2131.

The Applicant has amended independent claim 1 to read:

> A profile array substrate comprising:
>
> a first location for placement of a test tissue,

a second location for placement of ~~An~~a control oncology tissue microarray comprising a plurality of samples, each sample stably associated with a distinct, known sublocation on a substrate, at least one sample comprising a normal sample~~abnormally proliferating cells~~, the control oncology tissue microarray comprising samples representing the progression of cancer from an early stage to an advanced stage, the substrate further comprising an identifier providing access to a database comprising information relating to ~~at least one~~ each patient from whom ~~at least one~~ each sample of the control oncology tissue microarray was obtained,

wherein the profile array substrate allows testing of the test tissue to be done simultaneously with the testing of the samples on the control oncology tissue microarray allowing for a side-by-side comparison of the test tissue with the samples in the control oncology tissue microarray~~each sample of the microarray exhibits a biological characteristic representative of a stage of cancer~~.

The preamble of the claim has been amended to better clarify that the present invention comprises a first location for placement of an unknown sample (e.g., a patient in need of diagnosis) and a second location for the control oncology tissue microarray.

Support for the claim amendments can be found throughout the specification. More specifically:

> In one aspect of the invention, **a profile array substrate** is provided comprising **a first location for placement of a test tissue and a second location comprising a microarray**. In this aspect, the biological characteristics of a test tissue can be evaluated at the same time and under the same conditions as the biological characteristics of the cells/tissues within the microarray. (Page 4, Lines 10-13)(Emphasis added).

> As shown in Figure 2B, the substrate also can be configured as a **profile array substrate designed to accommodate a control microarray (a microarray comprising cell and/or tissue samples for which at least one biological characteristic being assayed for is known) and a test sample for comparison with the control microarray.** Profile array substrates generally comprise a first location for placing a test sample and a second location comprising the microarray. In this aspect, the first location is for placing a test tissue sample while the second sublocation comprises the microarray. **The profile array substrate allows testing of a test tissue sample to be done simultaneously with the testing of samples on the control microarray allowing for a side-by-side comparison of biological characteristics of**

> **the test sample with the characteristics of the cells/tissues in the microarray**. (Page 17, Lines 11-19)(Emphasis added).
>
> ...In another aspect of the invention, at least one sublocation of the microarray comprises a cancer cell. Preferably, the microarray comprises a plurality of different types of cancer (e.g., from different tissues), while in another aspect of the invention, different grades of the same cancer are provided on the same microarray. **More preferably, at least one sublocation comprises a healthy or normal tissue or cell sample**. (Page 3, Lines 15-19)(Emphasis added).
>
> The microarrays according to the invention comprise a plurality of sublocations, each sublocation comprising a cell or tissue sample having at least one known biological characteristic (e.g., such as cell or tissue type) which is stably associated with a substrate at the sublocation. **In a preferred aspect of the invention, the plurality of sublocations comprise cancerous tissue at different neoplastic stages**. The sublocations are distinct from each other in that they are separated by regions of substrate with no sample stably associated therewith. (Page 16, Lines 14-19)(Emphasis added).
>
> Generally, the order of donor samples within a recipient block can be varied to suit a user's needs. In a preferred aspect, microarrays comprise a plurality of tumor samples and different grades or stages of each tumor are represented on the array. Preferably, normal cell and/or tissue samples are provided in the recipient block as well. **Still more preferably, samples represent the progression of cancer from its earliest stage to its most advanced.** Samples can also be arranged according to treatment approach, treatment outcome or prognosis, or according to any other scheme that facilitates the subsequent analysis of the samples and the data associated with them. (Page 37, Line 28-Page 38, Line 4)(Emphasis added).

As such, the Applicant's amended claim 1 recites a profile array substrate comprising a first location for placement of a tissue sample. Further, the profile array substrate comprises a second location for placement of **a control oncology tissue microarray**. The control oncology tissue microarray comprises a normal (non-cancerous) tissue sample and further comprises a plurality of samples representing the progression of a type of cancer from an early stage to an advanced stage. As such, the profile array substrate allows for a "side-by side" comparison (morphology, biomarkers, expression of proteins, etc.) of the test tissue to the various samples representing various stages of a type of cancer. Applicant believes these amendments distinguish the

Applicant's claimed invention over the cited art and respectfully requests reconsideration and allowance of pending claims 1-2, 9, 10 and 12-15.

Lincoln et al.:

The Office Action rejected claims 1, 2, 5, 6, 10-13, and 15-16 under 35 U.S.C. §102(e)(2) as being anticipated by U.S. Patent No. 6,553,317 ("the '317 patent") to Lincoln et al. The Lincoln et al. reference, entitled "Relational Database and System for Storing Information Relating To Biomolecular Sequences and Reagents," discloses a relational database system for storing biomolecular sequence information together with biological annotations detailing the source of the sequence information, and associated reagent information. While the '317 patent makes reference to the use of a "biological microarray", the Lincoln et al. reference does not disclose a tissue microarray and does not disclose any type of control oncology tissue microarray comprising a normal (non-cancerous) tissue sample and further comprising a plurality of samples representing the progression of a type of cancer from an early stage to an advanced stage. Therefore, the Applicant believes that independent claim 1, as amended, is not anticipated by the Lincoln et al. reference.

The Lincoln et al. reference discloses the use of a microarray in three passages. First, Lincoln et al. discloses:

> The present invention further provides a reagent clone identified by a process, at least partially implemented on a computer system, for establishing a set of reagent clones. The process involves grouping initial sequences of polynucleotide inserts in a plurality of clones into a master cluster, assembling the initial sequences of the master cluster into one or more contiguous sequences, such that relationships of sequences to each other in the master cluster are elucidated, and nominating at least one clone represented by a master cluster as a reagent clone, according to specified priority criteria. **A set of reagent clones may have a variety of uses including as hybridizable elements on a biological microarray.** (Col. 2, Line 66-Col. 3, Line 12)(Emphasis added).

In the above-identified passage, the Lincoln et al. reference is merely disclosing that the clones identified as a result of practicing the Lincoln et al. invention can be used as hybridizable elements (i.e., a molecular probe) with a microarray. The Lincoln et al. reference does not

appear to be disclosing a novel microarray; more specifically, the Lincoln et al. reference does not appear to disclose a control oncology tissue microarray comprising a normal (non-cancerous) tissue sample and further comprising a plurality of samples representing the progression of a type of cancer from an early stage to an advanced stage. Therefore, the Applicant believes that independent claim 1, as amended, is not anticipated by the above-identified passage of the Lincoln et al. reference.

Second, Lincoln et al. discloses:

> As noted above, in one aspect, the invention provides a set of reagents. As used herein, a reagent is a clone which has been selected from a library or libraries of clones based on criteria designed to identify clones which are good candidates for further research. **A reagent clone has been resequenced and verified so that, for example, it may be provided to third parties for further research. A reagent may be used, for example, to do additional sequencing on the clone insert; the clone may be placed in an expression vector to make its associated protein; the clone's expression may be monitored, for example, using a biological microarray or northern blot technique; the reagent may be used to identify (pull out) additional related clones; or a set of reagent clones may be used as hybridizable elements on a biological microarray**... (Col. 8, Line 57-Col. 9, Line 4)(Emphasis added).

Similar to the first identified passage, the second passage is discussing potential uses for the clones identified by the method of the Lincoln et al. invention. The second passage appears to be merely disclosing that the clones of the invention may be used as hybridizable elements in conjunction with a microarray or their expression may be observed through the use of a microarray. The Lincoln et al. reference does not appear to be disclosing a novel microarray; more specifically, the Lincoln et al. reference does not appear to disclose a control oncology tissue microarray comprising a normal (non-cancerous) tissue sample and further comprising a plurality of samples representing the progression of a type of cancer from an early stage to an advanced stage. Therefore, the Applicant believes that independent claim 1, as amended, is not anticipated by the above-identified passage of the Lincoln et al. reference.

Third, the Lincoln et al. reference discloses:

> **In a preferred embodiment, clones undergoing resequencing for verification are processed in groups ("lots") of 96 clones, one for each chamber of a 96-well plastic culture dish (each chamber/well is an indentation in the dish that can hold a liquid such as a bacterial culture separate from all the others). After verification, clones that "pass" are re-racked (transferred) into new lots for storage.** When reagent clones and associated data are provided to third parties, such as customers purchasing the clones for further research, the reagent clones are preferably shipped in these lots. A customer receiving clones and their sequences must know not only that the clone has been received, but also its precise location, if s/he is to make use of the reagent. Lot and Well information is recorded for each reagent clone that passes the post-nomination processing to tell the customer where to find the clone. (EG clone 1234567 is located in lot #14332, well #G03). (Col. 12, Lines 20-36)(Emphasis added).

The above-identified passage merely describes a method of resequencing a set of 96 clones in a 96 well dish as a method of efficient verification. However, the passage does not disclose a tissue microarray; more specifically, the above passage does not appear to disclose a control oncology tissue microarray comprising a normal (non-cancerous) tissue sample and further comprising a plurality of samples representing the progression of a type of cancer from an early stage to an advanced stage. Therefore, the Applicant believes that independent claim 1, as amended, is not anticipated by the above-identified passage of the Lincoln et al. reference.

As shown above, the Lincoln et al. reference merely discloses that the clones identified by the Lincoln et al. invention can be used in conjunction with microarrays--the clones can be used as hybridizable elements or the sequence of the clones may be verified by reproducing the clones in a 96 well dish. However, the reference does not disclose the use of a tissue microarray; further, the Lincoln et al. reference does not disclose a control oncology tissue microarray comprising a normal (non-cancerous) tissue sample and further comprising a plurality of samples representing the progression of a type of cancer from an early stage to an advanced stage. Therefore, the Applicant believes that the claims, as amended, are not anticipated by the above-identified passages of the Lincoln et al. reference. As such, the Applicant respectfully requests reconsideration and allowance of pending claims 1-2, 9, 10 and 12-15.

Claims Rejected Under 35 U.S.C. §103:

The Final Office Action rejected claims 1-16 under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 6,553,317 to Lincoln et al. in view of Schraml et al. (Clinical Cancer Research, August 1999, vol. 5, pages 1966-1975) and Lehman et al. (Cancer Research, February 2000, vol. 60, pages 1062-1069), stating:

> This rejection is maintained and reiterated for reasons of record. The amended phrase "wherein each sample of the micro array exhibits a biological characteristic representative of a stage of cancer" in claims 1, 3, and 4 is not addressed as it is considered NEW MATTER that must be deleted.
>
> Lincoln et al. describe the use of bioinformatics to study genes differentially expressed or commonly expressed in different tissues or cell lines, such as normal (normally proliferating cells) and cancerous tissue (abnormally proliferating cells) (col. 1, lines 46-48). Lincoln et al. describe using a microarray with multiple samples (col. 3, lines 10-12). Lincoln et al. describe processing clones in groups on a 96-well plastic culture dish with each chamber/well comprising an indentation in the dish to separate samples (col. 12, lines 20-25) which represents a stably associated samples with a distinct, known sub location on a substrate, as stated in instant claim 1. Lincoln et al. describe a barcode (identifier) for a lot or 96-well plate whose value is placed in a barcode field of a table in a database (col. 21, lines 30-41) which represents a substrate with an identifier that provides access to a database, as stated in instant claim 1. The samples in a plastic culture dish represent the sample (tissue or cells) being plastic-embedded, as stated in instant claim 10. The information on the plastic culture dish, including precise sample location with lot and well information, is recorded for each sample and given to customers (col. 12, lines 29-36). Lincoln et al. describe using a relational database system for storing biomolecular sequence information with biological annotations (col. 2, lines 14-20) including information identifying (identifiers) sequences (col. 2, lines 28-34). Lincoln et al. describe a system allowing a user to selectively view information regarding sequences and reagent specifications (col. 2, lines 34-37) including a graphical user interface where a query is entered and matches between query and information is displayed (col. 2, lines 46-50). Lincoln et al. describe using a relational database with tables (col. 15, lines 44-49) including a library table that includes records of each library in the gene expression database including an identifier (LibraryID) (col. 16, lines 7-9). Lincoln et al. describe the library table as having a "TissueID" attribute that is inherited from a "TissueSpecimen" table) and a "Tissue_Category" attribute as well as a

"Lib_Description" attribute including information such as tissue name, disease state, patient age/gender (col. 16, lines 6-32). Lincoln et al. describe providing further information about a donor in a "MedicalHistory" table including information such as a problem such as breast cancer, breast, and neoplasm (col. 20, lines 33-40), as stated in instant claim 6. Lincoln et al. describe using a network to which the network server and clients are connected (col. 13, lines 3-9). Lincoln et al. describe entries in various results screens may provide links to other information in the database (col. 23, lines 10-13) as stated in instant claim 2. Lincoln et al. describe each tissue specimen (as uniquely identified by TissueID) may have several diagnoses (i.e. normal, diseased, involved, cancerous) and each donor may provide multiple tissue specimens (col. 19, lines 35-67). This act of providing multiple tissue specimens that are "cancerous" or "involved" is reasonably interpreted to include specimens from sites of a secondary metastasis of cancer, as stated in instant claim 16. Lincoln et al. describe different development stages (col. 20, lines 13-14) as stated in claim 11. Lincoln et al. describe studying or monitoring drug resistance in certain tissue (col. 5, lines 1-3) which represents substantially homogeneous cells (as stated in instant claim 13) and samples from patients treated with a drug (as stated in instant claim 15). However, Lincoln et al. do not describe using frozen cells or tissue, bodily fluid, 10% samples from different tissues, five different tumor types, samples greater than about 0.6 mm in diameter, and cancer-specific markers.

Schraml et al. describe using tissue microarrays for gene amplification surveys in many different tissue types (title). Schraml et al. describe using a tissue microarray consisting of samples from 17 different tumor types with 397 individual tumors arrayed in a single paraffin block (representing at least about 10% of the samples of the microarray, as stated in instant claim 7) using minute tissue samples (diameter, 0.6 mm) (abstract and Figure 1) which is greater than about 0.6 mm in diameter, as stated in instant claims 7, 8, and 9. Schraml et al. describe finding gene markers (i.e. CCND1) amplified in breast and other cancerous tissue types (abstract and page 1966, col. 2, first paragraph), as stated in instant claims 6 and 14. Schraml et al. describe hundreds of samples are precisely arrayed in a new paraffin block (page 1966, col. 2, second paragraph) which represents stably associated samples with distinct, known sublocations on a substrate, as stated in instant claims 1 and 4. Schraml et al. describe the precise positioning of tissue specimens to enable the generation of multiple replicate array blocks, each having samples from the same tissue specimens at identical coordinates (page 1970, col. 2), as stated in instant claims 1 and 4. Schraml et al. describe using frozen tissue samples from primary tumors (abnormally proliferating cells) and normal tissues (normally proliferating cells) and embedding the specimens in

paraffin (page 1966, col. 2, third paragraph), as stated in instant claims 3, 5, and 10. Schraml et al. describe using tumors in different stages and grades, including 96 breast tumors (page 1967, col. 1, second paragraph), as stated in instant claims 11 and 12.

Lehman et al. describe studying breast cancer patients for activity of exon and intron base changes in the p53 gene (abstract). Lehman et al. describe patient information, such as age (abstract). Lehman et al. describe gene studies in response to drug treatment (abstract). In Table 1, Lehman et al. describe various statistics of patients including the stage of breast cancer. Lehman et al. describe coding the samples from patients and entering the information into a database (page 1063, col. 1, first paragraph). Lehman et al. describe collecting blood (bodily fluid) from breast cancer patients for analyses (page 1063, col. 1, first paragraph), as stated in instant claim 4. Lehman et al. describe using paraffin-embedded tumor specimens and samples from patients undergoing drug treatments (page 1068, col. 1, third paragraph), as stated in instant claims 10 and 15.

Lehman et al. state the identification of woman at risk for development of breast cancer will have important implications for the prevention of cancers, treatment strategies, and improved cure rates of these patients (page 1062, col. 2, third paragraph). Schraml et al. state their tissue microarray technology has the potential to greatly facilitate analysis of alterations in multiple tissue types (page 1966, col. 2, second paragraph). Schraml et al. state that tumor arrays are a powerful tool to rapidly screen different tumor types for gene copy number alterations (page 1966, col. 2, second paragraph). Schraml et al. state they have demonstrated the power of using minute arrayed tissue specimens for tumor screening (abstract). Lincoln et al. state bioinformatics includes methods to search databases quickly to analyze information and make predictions (col. 1, lines 31-37). Lincoln et al. state information manipulation has been made easier to perform and understand with the development of sophisticated computer database systems (col. 1, lines 62-64). It would have been obvious to one of ordinary skill in the art at the time the invention was made to make improvements to existing gene expression techniques tied to relational database systems, as stated by Lincoln et al., because even though these systems provide great power and flexibility in analyzing gene expression information, this technology is still in its infancy and further improvements are required to accelerate biological research for numerous applications (Lincoln et al. col. 2, lines 6-12). Therefore, it would have been obvious to one of ordinary skill in the art to improve efficiency of microarray analyses with minute frozen and bodily fluid samples from multiple cancer patients and multiple tumor types (as stated by Schraml et al. and Lehman et al.) and relaying such information of relational database systems (as stated by Lincoln et al.) in

> order to accelerate research and evaluation in therapeutic pharmaceutical development and other fields by providing broad amounts of important information to clients in an easy to perform and understand format, as stated by Lincoln et al. (col. 1, line 62 to col. 2, line 28).
>
> Thus, Lincoln et al., in view of Schraml et al. and Lehman et al., motivate the instant claims.
>
> Applicants state that Lehman et al. and Schraml et al. recitations of a microarray do not anticipate an oncology microarray wherein each sample exhibits a biological characteristic representative of a stage of cancer. This is found unpersuasive as such a microarray with *each* sample exhibiting a biological characteristic representative of a stage of cancer appears to be NEW MATTER and not specifically mentioned in the instant application. (July 26, 2004 Final Office Action; Pages 7-12).

As will be discussed in detail below, our analysis indicates that neither the Lehman et al. reference nor the Schraml et al. reference cures the deficiencies of the Lincoln et al. reference. More specifically, neither Lincoln et al., Lehman et al., nor Schraml et al., alone or in any combination, teach, disclose or suggest a control oncology tissue microarray comprising a normal (non-cancerous) tissue sample and further comprising a plurality of samples representing the progression of a type of cancer from an early stage to an advanced stage.

"Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art." M.P.E.P. 2143.01. "The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art." *In re Kotzab,* 217 F.3d 1365, 1370, 55 U.S.P.Q.2d 1313, 1317 (Fed. Cir. 2000). See also *In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 U.S.P.Q.2d 1941 (Fed. Cir. 1992); M.P.E.P. 2143.01.

Lehman et al.:

The Lehman et al. reference discloses the results of a study entitled, "Elevated Frequency and Functional Activity of a Specific Germ-Line *p53* Intron Mutation in Familial Breast Cancer." The study appears to have utilized microarray technology to simultaneously identify a

specific genetic mutation in a plurality of samples. As such, the Lehman et al. reference merely discloses a prior art type use of a microarray--the ability to perform a plurality of reactions at a single time to increase efficiency. The Lehman et al. reference merely discloses a microarray to simultaneously test samples from a number of patients to identify which of the patients has a mutation of interest. The Lehman et al. reference does not disclose a tissue microarray (DNA was isolated from blood sample, see below); more specifically, the Lehman et al. reference does not disclose a control oncology tissue microarray comprising a normal (non-cancerous) tissue sample and further comprising a plurality of samples representing the progression of a type of cancer from an early stage to an advanced stage. As such, the Lehman et al. reference does not cure the deficiencies of the above-discussed Lincoln et al. reference.

In obtaining samples, the Lehman et al. reference discloses the following:

> ...A protocol for the study was approved by the Human Investigations Committee at Yale University School of Medicine, and all patients signed a written informed consent form. Samples were coded and entered into a double-blinded database. The enrolled familial breast cancer patients underwent an extensive interview for complete family history with a three-generation pedigree profile. **After the interview, all enrolled patients underwent sterile phlebotomy, from which 10-15 ml of blood was collected for genomic DNA isolation from lymphocytes.** ((Lehman et al., pgs. 1062-1063)(Emphasis added).

As such, the Lehman et al. experiments did not use tissue microarrays; the Lehman et al. experiments were conducted by arraying genomic DNA obtained from blood samples. With this Response, claim 1 has been amended to limit the claim to "control oncology **tissue** microarrays".

Next, in discussing the use of microarray technology, the Lehman et al. reference discloses:

> ...Therefore, we investigated the frequency of both exon and intron germ-line p53 base changes in 42 breast cancer patients with a strong family history of breast cancer. **Purified DNA obtained from the 42 indexed cases was screened for germ-line p53 mutations in exons 2-11 and surrounding introns using a combination of intron based primers for PCR-SSCP analysis, direct sequencing, and microarray sequencing using the Affymetrix p53 gene chip methodology**...(Lehman et al., p. 1063)(Emphasis added).

As such, Lehman et al. merely discloses using microarray technology to efficiently sequence 42 samples to determine which of these 42 samples comprises a genetic mutation of interest. The Lehman et al. reference does not disclose a control oncology tissue microarray comprising a normal (non-cancerous) tissue sample and further comprising a plurality of samples representing the progression of a type of cancer from an early stage to an advanced stage. As such, the Lehman et al. reference does not cure the deficiency of the above-discussed Lincoln et al. reference. More specifically, neither the Lehman et al. reference nor the Lincoln et al. reference, alone or in any combination, disclose, teach or suggest a control oncology tissue microarray comprising a normal (non-cancerous) tissue sample and further comprising a plurality of samples representing the progression of a type of cancer from an early stage to an advanced stage. As such, the Applicant respectfully requests reconsideration and allowance of pending claims 1-2, 9, 10 and 12-15.

Schraml et al.:

The Schraml et al. reference discloses the use of a tissue microarray to identify three known oncogenes in a plurality of different types of cancerous tissue. In so doing, the Schraml et al. references teaches that a 0.6mm tissue size is adequate to obtain a homogeneous representation of a tissue. However, like the references discussed above, the Schraml et al. reference is merely utilizing a microarray to perform a series of experiments in rapid succession. Unlike the Schraml et al. reference, the Applicant has constructed a control oncology tissue microarray wherein the samples on the control tissue microarray represent the progression of a type of cancer from an early stage to an advanced stage. Such a control microarray allows a test tissue (sample from a patient unaware of his/her diagnosis) to be compared side-by-side to the control oncology tissue microarray. As such, the Schraml et al. reference, alone or in combination with any of the references discussed above, does not appear to disclose, teach or suggest the amended claims of the pending application.

The Schraml et al. reference discloses:

> Gene amplifications are common in many different tumor types and may confer diagnostic, prognostic, or therapeutic information for patient management. Tedious experiments are often required to determine

> which tumor types have amplifications of a specific oncogene. **To facilitate rapid screening for molecular alterations in many different malignancies, a tissue microarray consisting of samples from 17 different tumor types was generated. Altogether, 397 individual tumors were arrayed in a single paraffin block.** To determine whether results from the literature can be reproduced on minute tissue samples (diameter, 0.6mm), amplification of three extensively studied oncogenes (CCND1, CMYC, and ERBB2) was analyzed in three fluorescence in situ hybridization experiments from consecutive sections cut from the tissue microarray...(Schraml et al., Abstract)(Emphasis added).

As such, the Schraml et al. reference discloses the ability to achieve rapid screening with the use of a microarray (a well known characteristic of microarray technology) and the reference appears to validate the use of tissue sections of 0.6mm in diameter (the smaller the section, the more samples you can fit on a slide, leading to even faster screening times). Neither of these teachings discloses, suggests or makes obvious the Applicant's claimed invention of a control oncology tissue microarray representing the progression of a type of cancer from an early stage to an advanced stage. Such a control microarray allows a test tissue (sample from a patient unaware of his/her diagnosis) to be compared side-by-side to the control oncology tissue microarray. As such, the Schraml et al. reference, alone or in combination with any of the references discussed above, does not appear to disclose, teach or suggest the amended claims of the pending application.

With this Response, the Applicant has made an earnest effort to respond to all issues raised in the Office Action of July 26, 2004, and to place all claims in condition for allowance. The Applicant has amended independent claim 1 in an attempt to clearly define the Applicant's claimed invention. The above discussion illustrates the Applicant's belief that the cited references merely disclose known uses of microarray technology--i.e., increased speed and efficiency, the ability to perform many experiments at once, etc. None of the cited references, alone or in any combination, anticipate or make obvious the idea of utilizing microarray technology to provide a control tissue microarray comprising known samples wherein the samples represent the progression of a type of cancer from an early stage to an advanced stage. As such, the Applicant respectfully requests reconsideration and allowance of pending claims 1-2, 9, 10 and 12-15.

Applicant submits that all claims are allowable as written and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicant's attorney/agent would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney/agent of record.

Respectfully submitted,

Date: September 27, 2004

Name: Michael P. Doyle
Registration No.: 49,052
Customer No.: 29932
Palmer & Dodge LLP
111 Huntington Avenue
Boston, MA 02199-7613
Tel.: (617) 239-0100